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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,799	03/10/2004	Arpita I. Mehta	085802-0111	5611

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EXAMINER	
GROSS, CHRISTOPHER M	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,799	MEHTA ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER M. GROSS	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44 and 51-59* is/are pending in the application.

4a) Of the above claim(s) *6,8,10,13,16,18,19,28 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9,11,12,14,15,17,20-27,29-31,36-44 and 51-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/3/04;5/13/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Responsive to communications entered 5/13/2008; 8/1/2008; 8/4/2008. Claims 1-44, 51-59 are pending. Claims 6, 8, 10, 13,16, 18-19, 28, 32-35 are withdrawn. Claims 1-5, 7, 9, 11-12, 14-15, 17, 20-27, 29-31, 36-44, 51-59 are examined herein.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/13/2008 has been entered.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the prior application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See Transco Prods., Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994) [taken from MPEP 201.01]

The present application was filed 3/10/2004 and claims benefit of provisional application 60/453,629 filed 03/10/2003. Nevertheless, support for: broadening claims 1 and 51 by deletion of "the selected therapeutic agents *target* two or more different members of a protein signaling pathway;" the total amount of protein (amendment to

claim 39 on 5/13/2008); at the same or a lower dose (amendment to new claim 56 8/1/2008); determining a presence, absence or amount of signaling proteins (new claim 59 8/1/2008) are not disclosed in the earlier application. See also 35 USC 112 first paragraph rejection below concerning new matter.

Therefore 3/10/2004 is the date for the purposes of prior art concerning claims 1-5, 7, 9, 11-12, 14-15, 17, 20-27, 29-31, 36-44, 51-59.

Information Disclosure Statement

The references indicated in the 9/3/2004 as abstract only have been considered to extent of the abstract. The supplemental IDS filed 5/13/2008 has been considered in its entirety and includes the dates for the Brightman, Burkhardt and Igarashi references referred to as nos. 16,17 and 64 in the previous office action. Applicant asserts the Winters reference referred to as "122" in the last office action is a manuscript inadvertently submitted with the present application and was ultimately published in Cancer Research after 3/10/2004, thus does not constitute prior art.

Withdrawn Rejection(s)

The rejection of claims 1,2,7,14-15,20-23,36-39,41-42 under 35 U.S.C. 102(b) as being anticipated by **Bishop et al** (US Patent 6316462) is hereby withdrawn in view of applicant's amendments.

The rejection of claims 1,2,7,14-15,20-23,36-39,41-42 and 11-12 under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) in view of **Lubman et al** (US Patent Application 2005/0230315) is hereby withdrawn in view of applicant's amendments.

The rejection of claims 1,2,7,14-15,20-23,36-39,41-42 and 43-44 under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) in view of **Moller et al** (US Patent 6,626,044) is hereby withdrawn in view of applicant's amendments.

The rejection of claims 1,2,7,14-15,20-23,36-39,41-42 and 3-5,9 and 17 under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) in view of **Bonner et al** (US Patent 6,251,516) is hereby withdrawn in view of applicant's amendments.

The rejection of claims 1,2,7,14-15,20-23,36-39,41-42 and 26,27,29-31 under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) in view of **Bilodeau et al** (US Patent Application 2002/0137755) as evidenced by Tortora et al (Clinical Cancer Research 9:1566-1572) is hereby withdrawn in view of applicant's amendments.

The rejection of claim 40 under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) **in view of Bilodeau et al** (US Patent Application 2002/0137755) as applied to claims 1,2,7,14-15,20-23,36-39,41-42 and 26,27,29-31 above, and further in view of **Bonner et al** (US Patent 6,251,516) as evidenced by Tortora et al (Clinical Cancer Research 9:1566-1572) and Moon et al (US Patent Application 2005/0282849) is hereby withdrawn in view of applicant's amendments.

The rejection of claims 1,2,7,14-15,20-23,36-39,41-42 and 25 under 35 U.S.C. 103(a) as being unpatentable over **Bishop et al** (US Patent 6,316,462) in view of **Jain**

et al (2000 IEEE Transactions on Pattern Analysis and Machine Intelligence 22:4-37 – IDS entry 9/3/2004) is hereby withdrawn in view of applicant's amendments.

The rejection of claims 51-55 under 35 U.S.C. 103(a) as being unpatentable over **Paweletz et al** (2001 Oncogene 20:1981-1989 - IDS entry 9/3/2004) in view of **Bishop et al** (US Patent 6,316,462) is hereby withdrawn in view of applicant's amendments.

The rejection of claims 3-5,11-12 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is hereby withdrawn in view of applicant's amendments.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5,7,9,11,12,14,15,17,20-27,36-38,39,41-44,51-59 are rejected under 35 U.S.C. 102(b) as being anticipated by **Petricoin et al** (2002 Nature Reviews/Drug Discovery 1:683-695 – IDS entry 9/3/2004).

The claimed subject matter per claim 1 is drawn to a method for selecting a combination of therapeutic agents for treatment of a disease caused by an abnormal cell signaling pathway or cell signaling pathway network that leads to an aberrant cellular response, comprising:

measuring activity states for a plurality of different signaling proteins extracted from a diseased cell obtained from a tissue of a subject, wherein the signaling proteins are members of one or more signaling pathways or networks;

measuring activity states for a plurality of different signaling proteins extracted from a reference cell, wherein the signaling proteins are members of one or more signaling pathways or networks;

determining whether the activity states measured for the plurality of signaling proteins extracted from the diseased cell are different than activity states measured for corresponding signaling proteins from the reference cell to detect differences between the activity states of individual signaling proteins from the diseased cell and the activity states of the corresponding individual signaling proteins from the reference cell; and

selecting a combination of at least two different therapeutic agents for the subject, wherein the agents reduce the difference that was detected in the activity states of the individual signaling proteins from the diseased cell compared to the reference cell.

Claims 2-5,7,9,11,12,14,15,17,20-27,36-38,39,41-44,51-59represent variations thereof.

Petricoin et al teach, throughout the document and especially the title and figure 9, how clinical proteomics may be applied to cancer patient management.

Petricoin et al teach in figures 1 and box 1 various protein signaling pathways that may be analyzed by cluster analysis, etc. which involves comparing proteomic patterns found in cancer vs. benign or unaffected specimens, therein providing measuring activity states for a plurality of different signaling proteins extracted from a diseased cell obtained from a tissue of a subject wherein the signaling proteins are members of one or more signaling pathways or networks as set forth in claims 1, 51 and 56 as well as measuring activity states for a plurality of different signaling proteins

extracted from a reference cell, wherein the signaling proteins are members of one or more signaling pathways or networks as set forth in claims 1 and 56. In figure 6, by comparing cancer tumor ERK and AKT phosphorylation to normal cells by way of laser capture microdissection in concert with a reverse-phase protein microarray based analysis, Petricoin et al determine whether the activity states measured for the plurality of signaling proteins extracted from the diseased cell are different than activity states measured for corresponding signaling proteins from the reference cell to detect differences between the activity states of individual signaling proteins from the diseased cell and the activity states of the corresponding individual signaling proteins from a reference cell per claims 1 and 51. In the section entitled Personalized Medicine starting on p 692, Petricoin et al teach selecting a combination of at least two different therapeutic agents for a subject, wherein the agents reduce the difference that was detected in the activity states of the individual signaling proteins from the diseased cell compared to the reference cell, as set forth in claim 1.

Petricoin et al teach combination therapy in figure 8 such that the amount two drugs required for effective therapy is less than either alone, reading on the synergistic improvement of claims 2, 51 last six lines and "at a lower dose" as set forth in amended claim 56. Also discussed in the legend to figure 8 is how combination therapy prevents shunting around a single pathway, as set forth in claim 27.

Said laser capture microdissection (elected species) reads on claims 3,4,5,7,9,53,54.

Said reverse-phase protein microarray (elected species) reads on claims 11, 58, 51 lines 11-14 and involves measuring antibody-phosphoprotein interactions, which is a protein-protein interaction per claim 22. The amount of phosphoprotein is compared by Petricoin et al in figure 6B to the total amount of signaling protein, reading on claim 39 and new claim 59.

Said comparison of ERK and AKT phosphorylation uses phosphoprotein specific antibodies, reading on claim 12. As shown in figure 6c, the phosphorylation of AKT is increased in tumor samples as compared to normal cells, which reads on claims 41-42, 57. Also shown in figure 6Bc, the phosphorylation of ERK is decreased in tumor samples as compared to normal cells, which reads on claims 43-44,57. Said ERK and AKT are in one or more signaling pathways or networks in accordance with figure 1 of Petricoin et al, reading on claims 55, and 56 lines 6 and 8-9.

Said cancer tumor and normal cells (elected species) are from the same subject, therein reading on claims 14-15, 17 and 52.

Petricoin et al teach monitoring the success of a therapy in figure 9, which inherently would include the administration set forth in claim 20.

Said cancer tumor reads on the abnormal growth (elected species) and cancer, as set forth in claims 21 and 36 respectively.

Petricoin et al teach on p 684, left column line 9 that proteomics may be applied toward diagnosing breast, lung or colon cancer, reading on claim 37.

Said comparison of ERK phosphorylation is a post-translational modification (elected species), reading on claims 23 and 56 lines 10-12.

Petricoin et al teach in the penultimate paragraph on p 694 how proteomic *pattern* analysis may be used to predict (based on prior results) which lead compounds under drug development should be taken forward or shelved, which reads on claim 24. This passage plus said cluster analysis, etc reads on claim 25.

Petricoin et al teach non-voltage gated calcium channels (Cadherins) and EGFR phosphorylation (elected species) and in figure 2, reading on claim 26.

Figures 1 or 2 of Petricoin et al read on the AKT signaling pathway, at least, set forth in claim 38.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5,7,9,11,12,14,15,17,20-27,36-38,39,41-44,51-59 and 29-31,40 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Petricoin et al** (2002 Nature Reviews/Drug Discovery 1:683-695 – IDS entry 9/3/2004) in view of **Hartman et al** (WO 2004/041164)

Petricoin et al is relied on as above.

Petricoin et al do not teach: a drug combination comprising carboxyamidotriazole (CaI) plus a specific COX 2 inhibitor such as Celecoxib, as set forth in claims 29-31; or one additional therapeutic agent, as set forth in claim 40.

Hartman et al teach, throughout the document and especially p 5 kinase inhibitors with formula I. Said kinase inhibitor is taken as the additional therapeutic agent set forth in claim 40. Hartman et al teach on p 17 lines 31-32 that it is especially desirable to include angiogenesis inhibitors therewith. Hartman et al teach on p 23 first and last paragraphs that angiogenesis inhibitors include CaI and nonsteroidal anti-inflammatories (NSAIDs) such as the COX 2 inhibitor Celecoxib, shown as the top structure on p 25.

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to apply laser capture microdissection in concert with a reverse-phase protein microarray per Petricoin et al toward judging the efficacy of the kinase inhibitor with or without the angiogenesis inhibitors described by Hartman et al.

One of ordinary skill in the art would have been motivated to apply laser capture microdissection in concert with a reverse-phase protein microarray per Petricoin et al

toward judging the efficacy of the kinase inhibitor with or without the angiogenesis inhibitors described by Hartman et al because, by monitoring the proteomic signature of an *individual* patient, it would allow for *personalized* medicine - in so far as it would provide for real time assessment of therapeutic efficacy and/or toxicity and rational redirection of therapy if needed for the patient - as noted by Petricoin in the last paragraph on p 694.

One of ordinary skill in the art would have had a reasonable expectation of success in applying the laser capture microdissection and reverse-phase protein microarrays of Petricoin et al toward the need for determining an efficacious amount of the kinase inhibitor with or without the angiogenesis inhibitors reported by Hartman et al because both references relate to blocking signaling cascades. In other words the kinase inhibitors according to Hartman et al fall squarely in the scope of technology of Petricoin et al.

Thus the claimed invention was within the ordinary skill in the art to make and use at the time the claimed invention was made and was as a whole, *prima facie* obvious.

New Claim Rejection(s) – 35 USC § 112

The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 9, 11-12, 14-15, 17, 20-27, 29-31, 36-44, 51-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description

requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection concerns "new matter."

5/13/2008 Amendment

Claims 1 and 51, as amended, delete "the selected therapeutic agents *target* two or more different members of a protein signaling pathway." The claims are now broader in the sense that the therapeutic agents may target just about any molecule in the cell. New claim 56 suffers from the same issue.

Claim 39, as amended adds the limitation that the phosphorylated signaling protein may be compared to the total amount of protein [in the cell].

In the remarks entered 5/13/2008, applicant attempts to point to support in original claim 2, p 8 lines 23-24 and p 55 line 19.

In this regard the following is noted. Original claim 2 being dependent from original claim 1 required the two therapeutic agents be targeted in the manner of original claim 1 (i.e. to two or more different members of a protein signaling pathway) and therein does not provide support for amended claims 1, 51 or new claim 56.

Page 8 lines 23-24 reads "tumor cells such as breast tumor cells, colon tumor cells, prostate cancer cells, and lung cancer cells. Still other examples of diseased cells include brain cells in which amyloid," Page 55 line 19 concerns EGF stimulated ATCC CCL-250 cancer cells. Accordingly is not clear how these passages provide support for the offending 5/13/2008 claim amendments.

8/1/2008 Amendment

Claim 56, as amended on 8/1/2008 adds the limitation of therapeutic agents being provided at the same or lower dose.

New claim 59, recites the limitation of measuring activity sates of signaling proteins by determining their presence, absence or amount.

In the remarks entered 8/1/2008, applicant attempts to point to support on p 10 line 4 to p 11 line 12. However the examiner does not find support for therapeutic agents being provided at the same or lower dose nor measuring activity sates of signaling proteins by determining their presence, absence or amount in the passage cited by applicant. Accordingly is not clear how these passages provide support for the offending 8/1/2008 claim amendments.

The specification as originally filed provided no implicit or explicit support for the above amendments. Similarly, the priority document (Provisional application 60/453,629) does not provide any implicit or explicit support for the limitations added or deleted from the claims.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the disclosure. See MPEP 714.02, paragraph 5, last sentence and also MPEP 2163.06 I.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a

claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure.*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER M. GROSS whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571 272 0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher M Gross
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cg

/ Christopher S. F. Low /
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